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Meta-analysis of randomized controlled trials on primary ambulatory thromboprophylaxis in patients with nonpancreatic gastrointestinal cancers receiving chemotherapy

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ABSTRACT

Primary ambulatory thromboprophylaxis (PATP) in patients with solid malignancies is not routinely indicated. We performed a meta-analysis of randomized controlled trials (RCTs) to determine the benefit and risk of PATP in patients with nonpancreatic gastrointestinal cancers receiving chemotherapy. RCTs with venous thromboembolism (VTE) reduction as primary or secondary endpoints were included. A total of 1932 patients from subgroups of 3 RCTs were eligible. The VTE incidence was 1.26% and 2.55% in PATP and control arms, respectively (risk ratio 0.49; confidence interval 0.25 to 0.96; $P = 0.04$), with a number needed to treat of 78 to prevent one VTE event. In gastric and gastroesophageal junction cancer patients, the VTE incidence was 1.37% and 3.40% in PATP and control arms, respectively (risk ratio 0.40; confidence interval 0.13 to 1.24; $P = 0.11$). PATP should not be recommended in patients with nonpancreatic gastrointestinal cancers on chemotherapy.

KEYWORDS Ambulatory thromboprophylaxis; colorectal cancer; gastric cancer; gastroesophageal junctional cancer; meta-analysis; venous thromboembolism

Cancer patients are 4 to 7 times more likely to develop venous thromboembolism (VTE) compared with noncancer patients.[1,2] VTE events are burdensome due to significant morbidity and decreased survival.[3,4] One retrospective study showed that thrombosis is the second leading cause of death after cancer progression itself in cancer patients.[5] Nonpancreatic gastrointestinal cancers (NPGCs) are associated with a high risk of VTE.[2,4] There is modest benefit of primary ambulatory thromboprophylaxis (PATP) in patients with solid cancers undergoing chemotherapy.[6,7] The Khorana score is a well-known VTE risk assessment tool in the ambulatory setting and has been used by some international guidelines to select high-risk cancer patients.[8,9] Pancreas cancer has the highest thrombogenicity, and meta-analyses for PATP in pancreas cancer were recently published.[10,11] Herein, we conducted a systematic review and meta-analysis to determine the benefit and risk of PATP in patients with NPGCs since the majority of NPGCs such as gastric cancers have high Khorana scores.[8]

METHODS

We performed the systematic review based on the *Cochrane Handbook for Systematic Reviews*[12] and reported it in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" guidelines.[13]

The terms "thromboprophylaxis" OR "anticoagulation" OR "low-molecular-weight heparin" OR "direct oral anticoagulants" AND "gastrointestinal cancer" were included in our search strategy through MEDLINE and EMBASE databases until May 31, 2021. We also hand-searched abstracts from the major oncology conferences, especially those of the American Society of Clinical Oncology and the European

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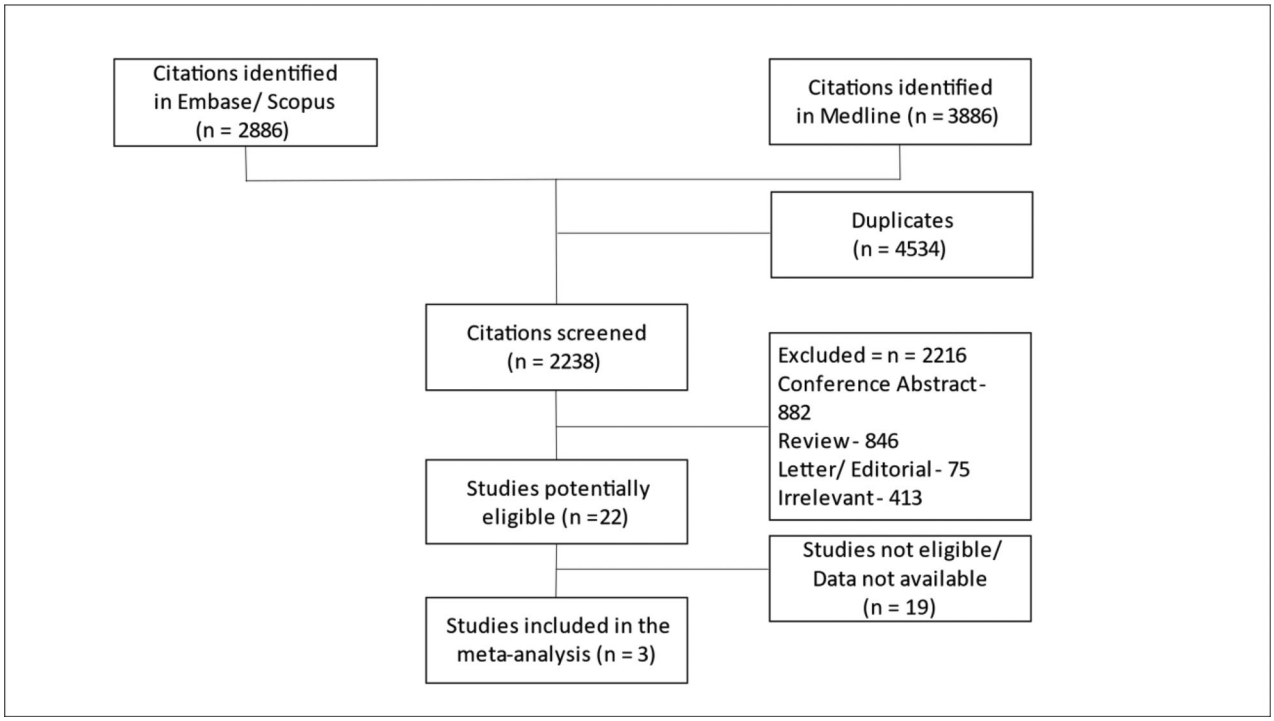

Figure 1. Study flow diagram in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA).

Society of Medical Oncology. We limited the database search to "humans" and "controlled clinical trials," and randomized controlled trials (RCTs) written in English were retrieved. We evaluated the titles and abstracts of the relevant citations and included all potential studies that were pertinent to our topic through the references of research articles.

To be eligible for inclusion in the meta-analysis, studies had to conform with the following characteristics: RCTs comparing PATP with low-molecular-weight heparins or direct oral anticoagulants vs a control arm; RCTs of patients who were undergoing ambulatory chemotherapy for NPGCs; and RCTs with reduction in VTE as a primary or secondary endpoint and major hemorrhage as a safety outcome.

Two authors (T.W.H. and K.Z.T.) independently reviewed the titles and abstracts of all selected studies and extracted the data from each eligible study after the duplicates were removed. We collected the following data: first author's last name, published year, name and type of study, primary and secondary outcomes, types of cancers, dosage and duration of study anticoagulants, types of chemotherapy, number of patients included in each arm, and number of VTE events. Disagreements were resolved by consensus, in conjunction with the senior investigators (D.P.Q. and T.H.O.). Biases in each study were identified by using the tool recommended by the Cochrane Collaboration. Potential biases were categorized as selection bias, performance bias, detection bias, attrition bias, reporting bias, and other and were rated as low, high, or unclear risk.[14]

All analyses were performed using Review Manager, version 5.3 (Nordic Cochrane Center; Copenhagen, Denmark). The significance of the data was defined as P value < 0.05. I^2 statistic and Cochran's Q-statistic were used to assess heterogeneity among the studies.[14] The pooled risk ratio and risk difference with 95% confidence interval (CI) were calculated by using the fixed effects model with Mantel-Haenszel method as our primary meta-analytic approach. The aim of our meta-analysis was to determine the benefit and risk of PATP in patients with NPGCs receiving chemotherapy. Publication bias was assessed by funnel plots.

RESULTS

We identified 2238 potential references after 4534 duplicates were removed. A total of 22 records identified from the databases were assessed for eligibility for inclusion in our study. The final analysis incorporated three RCTs involving 1932 patients.[6,15,16] *Figure 1* shows the detailed steps of the systematic review process.

The characteristic features of included studies are summarized in *Table 1*. The prophylactic doses of nadroparin, semuloparin, or rivaroxaban were given to patients in the study arms for 3.5 to 6 months while the control arms utilized placebo. The randomization ratio was 2 to 1 in the Prophylaxis of Thromboembolism During Chemotherapy Trial, and 1 to 1 in the Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy Trial and the Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism (VTE) Prophylaxis in Ambulatory Cancer Participants Trial. All patients had gastric or gastroesophageal junction cancers or colorectal cancers.

The risk of bias for each study, evaluated by Cochrane RevMan 5.3 software, is depicted in *Figure 2*. Publication bias was not detected in the study.

Table 1. Characteristics of the studies included in the meta-analysis

Study (subgroup)/author (year)	Types of GI cancers	Patients (control/anticoagulant)	Anticoagulant (dose and duration)	Primary efficacy outcome measure
PROTECHT Agnelli et al (2009)	Stomach	40/58	Nadroparin 3800 IU daily for up to 4 months	Reduction in VTE
	Colon and rectum	108/214		
SAVE-ONCO Agnelli et al (2012)	Stomach	207/204	Semuloparin 20 mg daily for median of 3.5 months	Reduction in VTE
	Colon and rectum	461/464		
CASSINI Khorana et al (2019)	Stomach and gastro-esophageal	87/89	Rivaroxaban 10 mg daily for 180 days	Reduction in VTE

CASSINI indicates Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism (VTE) Prophylaxis in Ambulatory Cancer Participants Trial; GI, gastrointestinal; PROTECHT, Prophylaxis of Thromboembolism During Chemotherapy Trial; SAVE-ONCO, Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy Trial; VTE, venous thromboembolism.

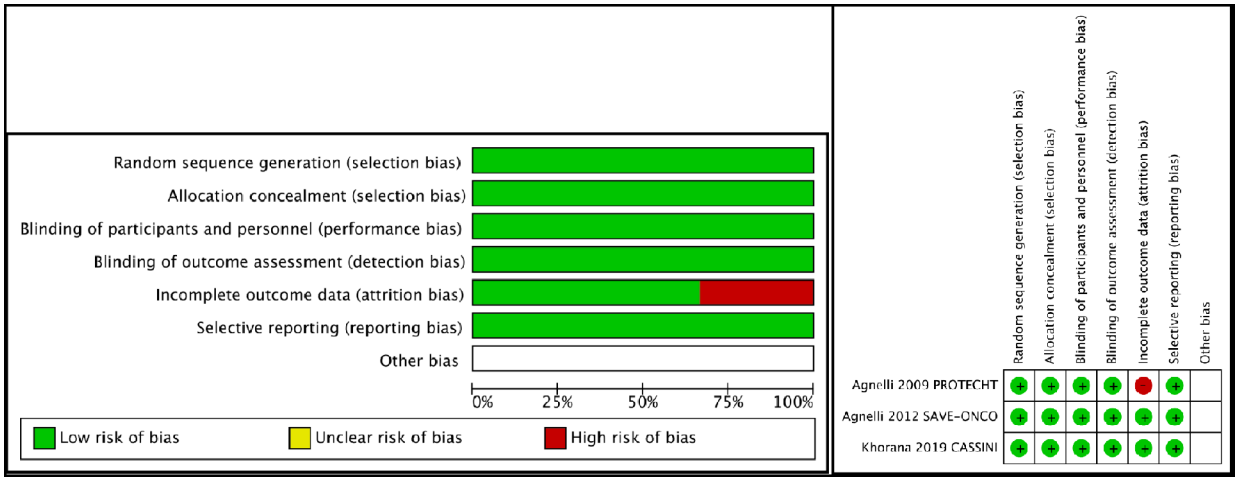

Figure 2. Risk of bias summary.

In patients with NPGCs, VTE events occurred in 13 patients (1.26%) and 23 patients (2.55%) in the PATP and control arms, respectively. The pooled risk ratio for VTE events was statistically significant at 0.49 (95% CI 0.25 to 0.96, $P = 0.04$). The absolute risk difference for VTE occurrence was −0.01 (95% CI −0.03 to 0.00, $P = 0.04$), with an estimated number needed to treat of 78 to prevent one VTE event *(Figure 3)*.

We performed subgroup analysis of the included studies for the occurrence of VTE in patients with gastric and gastroesophageal junction cancers. Among 587 patients with gastric and gastrointestinal junction cancers, the VTE incidence was 4 (1.37%) and 10 (3.40%) in the PATP and control arms, respectively, according to analysis of two RCTs. The pooled risk ratio was not statistically significant at 0.40 (95% CI 0.13 to 1.24, $P = 0.11$) *(Figure 4)*. In all three RCTs, there were no specific data for safety outcomes in each subset of cancer (gastric or gastroesophageal or colorectal cancers).

DISCUSSION

Diagnosis of VTE has a significant impact on health-related quality of life of cancer patients who are undergoing chemotherapy, with considerable morbidity and adverse outcomes.[3] A study from the Dutch Cancer Registry found that there was a 2.2 times higher rate of mortality in cancer patients with VTE than in those without VTE.[3] Chemotherapy is an additional risk factor, increasing VTE risk by 6.5-fold in cancer patients.[17] A retrospective 5-year cohort study by Khorana et al for VTE risk in hospitalized cancer patients showed a VTE risk of 4.9% in stomach, 4.3% in esophageal, and 3.5% to 4.0% in colorectal cancer patients.[18] Upper gastrointestinal malignancies are considered highly thrombogenic, and both the pancreas and stomach are assigned a Khorana score of 2.[8,19] Uncertainties also remain in terms of the survival benefit in other solid tumors despite lowering the VTE events. Recently, multiple trials have demonstrated that PATP significantly decreased VTE events without improvement in overall survival.[20–22]

The 2019 International Initiative on Thrombosis and Cancer recommended PATP with direct oral anticoagulants in ambulatory cancer patients receiving chemotherapy with an intermediate to high risk of VTE.[9] Based on findings from our meta-analysis, VTE events were not statistically significantly reduced by PATP in gastric and gastrointestinal

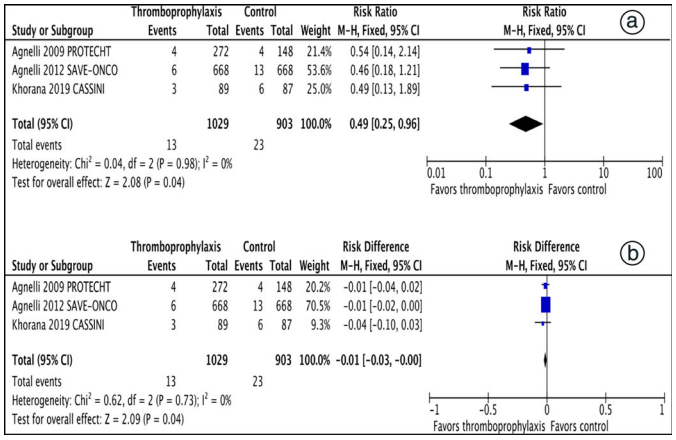

Figure 3. **(a)** Pooled risk ratio and **(b)** risk difference for venous thromboembolism in ambulatory patients with nonpancreatic gastrointestinal cancers receiving thromboprophylaxis vs control.

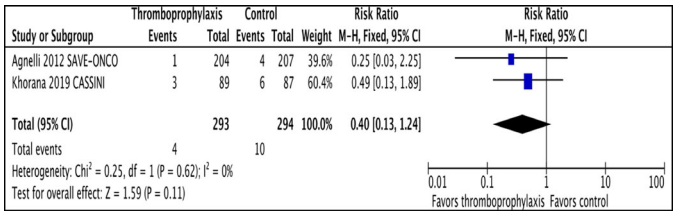

Figure 4. Pooled risk ratio for venous thromboembolism in ambulatory patients with gastric and gastroesophageal junction cancers receiving thromboprophylaxis vs control.

junction cancers (considered high risk by a Khorana score $\geq$ 2). Although PATP statistically significantly reduced VTE events in patients with NPGCs, 78 patients needed to be treated to prevent one VTE event, compared to a number needed to treat of 12 in pancreatic cancer patients and 25 in lung cancer patients.[10,23] We also reviewed the famous "Apixaban for Prevention of Venous Thromboembolism in Cancer Patients" trial results. However, the authors did not mention the specific data on the NPGCs.[24]

A recent meta-analysis pointed out that the Khorana score is designed to consider PATP for patients in the high-risk group, but only one-fourth of VTE events occur in the high-risk subset. In other words, a larger proportion of patients with subsequent VTE events will be missed by the Khorana score.[25] Another large retrospective cohort study conducted by Chaudhury et al showed that the vast majority of cancer patients with VTE were actually categorized as low risk according to Khorana score, and that a substantial number of patients would not receive thromboprophylaxis.[26] Hence, further studies are essential to improve risk stratification methods and to define high-risk subsets of NPGC patients receiving chemotherapy who may benefit from PATP. Considering health-related quality of life, cost burden, and lack of strong evidence, PATP should not be recommended in patients with NPGCs outside of the context of clinical trials, and more randomized studies are required to solidify the uncertainties.

In conclusion, in our study, the relative risk reduction was 48% with a number needed to treat of 78 to prevent one VTE event in ambulatory patients with NPGCs receiving chemotherapy. Nevertheless, there was no statistically significant reduction in VTE events in the high-risk subset of gastric and gastroesophageal junction cancers. Based on the findings, PATP is not recommended in patients with NPGCs on chemotherapy at this time.

CONFLICT OF INTEREST

Kyaw Zin Thein, Thura Win Htut, and Donald Quick declare no conflict of interest. Thein Hlaing Oo served on an advisory board for Bristol-Myers Squibb, not related to this manuscript.

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